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## **Tyloxapol confers durable protection against hyperoxic lung injury in the rat.**

**Sachs S, Ghio AJ, Young SL.**

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We tested the hypothesis that the nonlipid components of Exosurf, tyloxapol (TY), and cetyl alcohol (CA), protect against hyperoxic lung injury by induction of the animals' endogenous antioxidant defenses. Adult rats were intratracheally instilled with escalating doses of TY and CA (n = 20) or TY alone (n = 32) and immediately exposed to 100% oxygen. Intratracheal instillation of TY alone or in combination with CA protected against lethal hyperoxic injury in the rat in a dose-dependent fashion. To assess the effects of timing, rats were instilled with TY plus CA 24 hours before (n = 6) and 24 hours after (n = 6) exposure to 100% oxygen, with time to death determined. Rats were also instilled with TY alone at 0 hour (n = 6), 48 hours (n = 3), 96 hours (n = 3), and 186 hours (n = 4) prior to exposure to 100% oxygen. Lungs were assayed for superoxide dismutase, glutathione peroxidase, and catalase activities. Finally, the pharmacokinetics of TY in the rat lung were determined by instilling radiolabelled TY intratracheally. TY has a prolonged half-life in the rat lung, and protection against lethal hyperoxic injury was achieved by a single intratracheal dose delivered up to 186 hours prior to injury. Antioxidant enzymes were not induced in protected animals. We conclude that TY provides durable protection against hyperoxic lung injury without induction of antioxidant enzymes. It is present in the lung for sufficient duration to invoke a direct mechanism of protection, possibly as a radical scavenger. These findings raise the prospect of a therapeutic application for TY as prophylaxis in patients at risk for oxygen toxicity and adult respiratory distress syndrome.

PMID: 10533679 [PubMed - indexed for MEDLINE]

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## **[Many persons with snoring problems and apnea are untreated. A review of therapeutic methods]**

[Article in Swedish]

**Hultcrantz E.**

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Halskliniken, Akademiska sjukhuset, Uppsala. [elisabeth.hultcrantz@orl.uu.se](mailto:elisabeth.hultcrantz@orl.uu.se)

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As sleep apnoea and snoring are very disabling conditions both for patients and their families, and hazardous for drivers and others in traffic, there is good reason to treat snoring problems. Treatment should be individualised, always beginning conservatively--i.e., positional training, weight reduction if necessary, more sleep if sleep deficiency is present, and a review of any muscle-relaxant or mucolytic medication. Sleep registration will demonstrate the extent of any sleep apnoea syndrome, which is of decisive importance for further choice of treatment. Mild apnoics and social snorers may initially be offered an occlusal splint if their dental status allows. Otherwise, in such cases surgery is a form of treatment yielding immediate results, though the patient must be forewarned of the discomfort which can occur in isolated cases. For patients with sleep apnoea syndrome of marked or intermediate severity, continuous positive airway pressure (CPAP) treatment should be available. If the patient can not tolerate CPAP treatment, the occlusal splint alternative can be tried. For patients who can not have CPAP or occlusal splint treatment, tracheostomy is a possibility. This treatment may be lifelong, but if weight reduction is achieved postoperatively, it may be possible to remove the tracheostomy.

Publication Types:

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*Thorax* 2000;55:964-969 ( November )**Review series**

Paediatric origins of adult lung diseases • 3

**The genesis of adult sleep apnoea in childhood****F McNamara, C E Sullivan**

David Read Laboratory, Department of Medicine, University of Sydney, NSW 2006, Australia

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**▶ Introduction**

Obstructive sleep apnoea (OSA) and central sleep apnoea have been identified and described in adults, children, and infants.<sup>1-3</sup> It is not certain, however, if the adult sleep apnoea syndromes, particularly OSA, originate from childhood or whether paediatric and adult sleep apnoea are separate syndromes. Some investigators have suggested that the pathophysiology, criteria for diagnosis, and the management of paediatric patients with OSA are different from that for adults.<sup>4-7</sup>

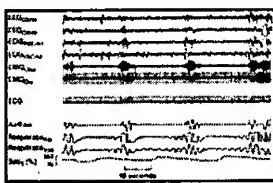
Other investigators have found that risk factors, clinical symptoms, and the consequences of OSA share common features between adults, children and infants.<sup>8-11</sup> We propose that the adult sleep apnoea syndrome is related to sleep apnoea in children, and that adult patients with sleep apnoea have been predisposed to developing apnoea since early infancy. The differences in OSA in patient populations of different age groups may represent different stages in the development of the adult form of OSA. This review will discuss the similarities and differences between adult, childhood and infant sleep apnoea, particularly OSA. The risk factors, potential mechanisms, and familial factors of OSA will be presented to ascertain the possible genesis of adult sleep apnoea during childhood.

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**▶ The sleep apnoea syndromes**

The OSA syndrome in adults was identified more than 30 years ago,<sup>12</sup> has been described extensively in adults, and is believed to be caused by collapse of the oropharyngeal airway.<sup>1</sup> It is not certain whether adult patients had OSA as infants or children; however, the diagnosis of OSA in adults often occurs several years after the onset of symptoms, sometimes starting during adolescence. Obstructive apnoea is associated with repetitive episodes of hypoxaemia, sleep fragmentation, and cardiovascular and neurobehavioural sequelae (fig 1).<sup>13-15</sup> Several risk factors have been identified that predispose an individual to developing OSA including obesity, age, sex, upper airway structural abnormalities, and a family history of OSA.<sup>11 16-19</sup>

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**Figure 1** Polygraphic example of repetitive obstructive apnoea. EEG<sub>C3/A2</sub> and EEG<sub>O2/A1</sub> = central and occipital electroencephalogram, respectively; EOG<sub>ROC/A1</sub> and EOG<sub>LOC/A2</sub> = right and left oculogram, respectively; EMG<sub>Chin</sub> = submental electromyogram; EMG<sub>Dia</sub> = diaphragm electromyogram; EMG<sub>Abd</sub> = abdominal electromyogram; ECG = electrocardiogram; Airflow = airway pressure measured from nasal prongs; Respitrace<sub>Rib</sub> and Respitrace<sub>Abd</sub> = thoracic and abdominal movements, respectively; SaO<sub>2</sub> = arterial oxyhaemoglobin saturation (%). Inspiration is an upward deflection on the airflow and Respitrace signals. Note that there is a cessation of airflow accompanied by continued deflections from the Respitrace channels. The apnoeas are associated with decreases in SaO<sub>2</sub> to approximately 75% and are terminated by brief arousals.

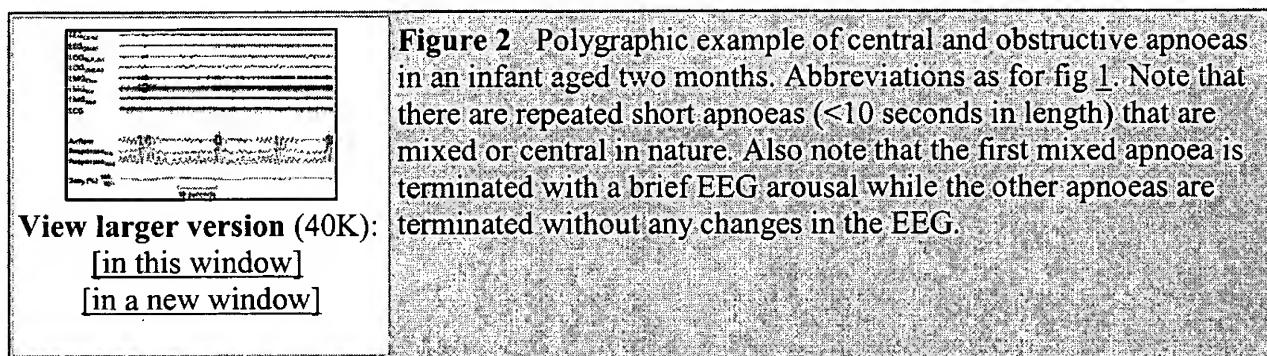
### SLEEP APNOEA IN INFANTS

During the first year of life, marked changes and development of the cardiorespiratory system occur in infants due to growth and maturation of the central nervous system.<sup>20</sup> Sleep apnoea is commonly recorded in infants; it is usually central in nature and is considered to be a normal manifestation of the immature central nervous system. Periodic breathing—that is, episodes of repetitive central apnoea—is also a common pattern of apnoea recorded in infants. Central sleep apnoea and periodic breathing during non-REM and REM sleep occur most frequently during the neonatal period and decrease in frequency during the first 6-12 months of life.<sup>21-25</sup>

OSA has been thought to be rare in infants and few data exist on the occurrence of OSA in normal infants. Upper airway obstruction has been hypothesised to occur in association with craniofacial abnormalities—for example, Pierre Robin sequence,<sup>26</sup> apnoea of prematurity,<sup>27</sup> and apparent life threatening events (ALTE).<sup>28</sup> OSA has also been implicated in the mechanisms of the sudden infant death syndrome (SIDS).<sup>29-31</sup> The mechanisms of airway obstruction in infants are not certain. In preterm infants it has been suggested that airway closure is caused by decreased upper airway muscle tone.<sup>32</sup> Endoscopic examination of the upper airway during obstructive apnoea in infants with ALTE has shown

that obstruction occurs at the level of the larynx,<sup>28</sup> similar to that observed in adults.<sup>1</sup>

The occurrence of obstructive and central sleep apnoea in some infants has been shown to change during the first year of life (fig 2). In a group of infants with OSA who had either experienced an ALTE or had a family history of SIDS it was found that OSA peaked in severity at approximately two months of age and subsequently improved and resolved with age.<sup>33</sup> Their apnoea was dominated by periodic breathing involving predominantly mixed apnoea, a pattern not unlike the repetitive obstructive apnoeas recorded in adults. This supports the speculation that OSA in paediatric patients is a precursor for adult OSA. Although the apnoea resolved with development, it is possible that infants with this pattern of apnoea during the first year of life may be predisposed to upper airway obstruction and may therefore be likely to develop OSA later in life.



#### SIDS, ALTE AND ITS ASSOCIATION WITH OSA

It has been suggested that SIDS, ALTE, and OSA in infants have similar pathophysiological mechanisms and recently these have been linked to the adult OSA syndrome.<sup>34-37</sup> Obstructive and central apnoea has been recorded during sleep in infants who have experienced an ALTE.<sup>28 34 35</sup> In addition, several studies have reported obstructive events during sleep in infants who subsequently became victims of SIDS.<sup>29-31</sup> Guilleminault *et al*<sup>30</sup> were the first to document obstructive apnoea in an infant with laryngomalacia who subsequently died of SIDS. Kahn *et al*<sup>29</sup> and later Schlüter *et al*<sup>31</sup> found that infants who subsequently died of SIDS had obstructive events more commonly recorded on a previous polysomnographic study than matched controls or infants who died from other known causes. These findings have suggested that upper airway obstruction is probably involved in the mechanisms of SIDS and ALTE.

More recently Rees *et al*<sup>38</sup> have presented further evidence that infantile OSA, SIDS, and the adult OSA syndrome are related. These investigators found differences in the facial structure of infants who died of SIDS compared with control infants. The anatomical features found in the SIDS cases—namely, a retrognathic facial structure—would predispose these infants to narrowing and occlusion of their upper airways. This anatomical feature is similar to that found in many patients with the adult OSA syndrome. Facial structure is believed to be, at least in part, genetically inherited and it is likely that a predisposition to develop OSA either in childhood or adulthood has been determined prenatally.

#### OSA IN CHILDREN

Upper airway obstruction has been recorded in children and, although no population studies have been performed, it is now considered to be a common problem.<sup>39</sup> Polygraphic studies performed in children

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The association between childhood and infantile OSA is not certain; however, Guillemineault and colleagues<sup>43 44</sup> have reported the development of OSA from infancy to childhood. In a group of children who were first diagnosed with apnoea following an ALTE during the first four months of life, more florid symptoms of obstruction developed and they were diagnosed with OSA by five years of age. These reports suggest that the onset of obstructive sleep apnoea may occur very early in life.

The clinical symptoms and consequences of OSA vary between infants, children, and adults. In adults, regardless of when the diagnosis of OSA was confirmed, the onset of symptoms can often be traced back to adolescence or childhood. In adults the most common symptom includes daytime hypersomnolence which is believed to be caused by the sleep fragmentation associated with the repeated obstruction.<sup>13 45</sup> In contrast, excessive daytime sleepiness is not frequent in children who have OSA.<sup>5</sup> Behavioural problems such as hyperactivity and aggressiveness have been reported, and learning problems in school aged children can occur.<sup>2 46 47</sup> In infants the effect of OSA on daytime behaviour is difficult to measure; however, in infants whose OSA was treated with nasal continuous positive airway pressure (CPAP) parents reported a change in the infants' alertness during wakefulness following treatment.<sup>48</sup>

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OSA in adults is associated with repetitive arousals from sleep, terminating the obstructive event and resulting in sleep fragmentation.<sup>1 13</sup> However, the majority of apnoeas recorded in infants and children are resolved without any change in the EEG pattern.<sup>49</sup> The association of apnoea with arousal is age



related; a higher percentage of apnoeas are terminated with an arousal as age increases, suggesting a relationship between change with development of OSA and arousal between infants, children, and adults. It has been suggested that subcortical arousals may be important in infants and children.<sup>50 51</sup> Recently, however, it was found that termination of obstructive apnoea in adults, as in children, did not always occur with an EEG arousal and was sometimes accompanied by subcortical responses in the absence of an EEG arousal.<sup>52</sup>

The sleep disturbances in patients with OSA have significant effects on sleep architecture. In infants OSA is associated with shortened episodes of REM sleep and an overall decrease in the amount of REM sleep.<sup>33</sup> In contrast, in children OSA is associated with a decrease in slow wave sleep<sup>47</sup> and in adults a deficit of REM sleep and slow wave sleep have been associated with OSA.<sup>53</sup> When sleep apnoea is prevented by CPAP treatment or resolved with development, the sleep disturbances are at least partly reversed.<sup>48 53 54</sup>

Snoring during sleep is another predominant symptom in adults with OSA.<sup>13 45 55</sup> Snoring is also a common feature in children with OSA<sup>2 7 47</sup> but has rarely been reported to be associated with OSA in infants. However, Kahn *et al*<sup>10</sup> recorded snoring and noisy breathing in infants with obstructive apnoeas during sleep. The snoring in their study is possibly equivalent to the intermittent noisy or laborious breathing that has been described by other investigators.<sup>30 37 43</sup> In addition to snoring, other symptoms that were apparent in infants with abnormal breathing during sleep included breath holding spells, fatigue during feeding, and profuse sweating during sleep.<sup>10</sup> OSA symptoms in children reported by parents include sweating, restlessness during sleep, frequent awakenings and, in some cases, nocturnal enuresis.<sup>2 47 56</sup>

More recently the focus of OSA has been on the cardiovascular consequences, in particular the effect of obstructive apnoea on blood pressure responses. OSA in adults is associated with an increased frequency of systemic hypertension.<sup>57 58</sup> Pulmonary hypertension has been recorded in children with OSA but systemic hypertension secondary to OSA is thought to be uncommon in children.<sup>7</sup> This could indicate that the haemodynamic effects of OSA are the result of a prolonged disease or that they were not recognised in children. Recently, however, OSA in children was found to be associated with an increased diastolic blood pressure and the increase in blood pressure could be predicted by the apnoea index and body mass index.<sup>9</sup>

## ► Risk factors for OSA

Obesity is reported in a high proportion of adult patients with OSA<sup>13 59</sup> but is not always found in paediatric patients with OSA, with varying prevalences of OSA being reported in obese children.<sup>60 61</sup> A high prevalence of OSA has been recorded in overweight infants in the absence of clinical symptoms.<sup>62</sup> In infants and young children, however, failure to thrive is commonly associated with OSA<sup>63</sup> and relief of the OSA by surgery or CPAP treatment often results in "catch up"

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growth.<sup>2 54 64</sup>

In adults the incidence of OSA increases with age and is more common in men. Approximately 9% and 4% of middle aged men and women, respectively, are reported to have OSA.<sup>14</sup> In children the prevalence of OSA has been studied in children up to six years of age using overnight video recording and oximetry and questionnaires. Approximately 1% of children of pre-school age are believed to have OSA<sup>7</sup> and there is conflicting evidence about its sex distribution. Carroll and Loughlin<sup>5</sup> reported that there was no sex difference in children with OSA; however, Marcus *et al*<sup>2</sup> found that OSA was more common in boys. There are no reliable data on the prevalence of OSA or any sex differences during infancy. In SIDS victims, however, there is a male predominance with approximately 60% of cases being boys.<sup>65</sup>

Other less common risk factors may vary among the different patient groups. Structural malformation of the brainstem that occurs in myelomeningocele, for example, is associated with obstructive and central apnoea.<sup>66</sup> Respiratory infections and allergic rhinitis can exacerbate and induce obstructive apnoeas in children and adult patients.<sup>61 67</sup> In infants a viral respiratory infection such as respiratory syncytial virus can cause life threatening obstructive apnoea.<sup>68</sup> These findings suggest that increased nasal resistance and airway inflammation may be involved in the pathogenesis of OSA in all patients.

## ► Structural abnormalities and OSA

Potential causes of OSA include anatomical abnormalities of the face and upper airway. The anatomical features may involve the bone or the mucosa and soft tissue development and structure. Some investigators have suggested that the existence of any anatomical features leading to a narrow upper airway may favour the development of sleep disordered breathing from early infancy to adulthood.<sup>44</sup>

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OSA is common in infants and children who have anatomical abnormalities involving the face, mandible, and the size of the upper airway. These abnormalities include laryngomalacia; mid face hypoplasia that occurs, for example, with Down's syndrome; or the micrognathia, cleft palate, and macroglossia that occurs in the Pierre Robin sequence.<sup>69 70</sup> The obstruction in these infants and children is often relieved by surgery to correct the site of obstruction; however, follow up of these patients to ensure that OSA does not return with age has been limited.

Adenotonsillar hypertrophy is frequently assumed to be the predominant cause of childhood OSA, and removal of the tonsils and adenoids usually results in relief of obstructive symptoms.<sup>2 46 47 71</sup> Some children, however, continue to have residual OSA following adenotonsillectomy.<sup>72</sup> In addition, the severity of the OSA before surgery is not always proportional to the size of the tonsils and adenoids.<sup>73 74</sup> These findings suggest that other factors such as abnormal ventilatory drive, mechanical abnormalities, and other anatomical abnormalities of the upper airway may be involved in the mechanisms of OSA. In reality the size of the tonsils and adenoids is rarely the primary problem. The severity of OSA has been reported to be inversely related to the size of the posterior airway<sup>74</sup>; other investigators have shown that



children with OSA have a more collapsible upper airway than age matched controls<sup>75</sup> and similar findings have been reported in adults.<sup>76</sup>

A prospective cohort investigation of prepubertal children with OSA found that the symptoms resolved 2-4 months after tonsillectomy but that apnoeas during sleep recurred years later at puberty.<sup>77</sup> Cephalometric radiography indicated a reduced posterior airway space in these children. The upper airway and craniofacial anatomy are influenced by genetic factors and the development of OSA may be predetermined from childhood. Evaluation of upper airway and craniofacial morphology in children with OSA may identify patients at risk of persisting or recurring symptoms later in life. It is possible that OSA originates from prenatal factors that will lead to a development of OSA at various stages throughout life.

## ► Familial OSA syndrome

There is significant evidence that familial factors influence the risk of developing upper airway obstruction in both paediatric and adult patients. OSA in adults has been shown to aggregate significantly within some families.<sup>19 78-82</sup> The familial occurrence of OSA was first described by Strohl *et al*<sup>78</sup> who reported OSA in several members of one family. In addition, an infant of this family had died of SIDS and it was speculated that SIDS may have been related to the familial

OSA. Family studies have shown that relatives of patients with OSA have a 2-4 fold increased risk of developing OSA compared with controls.<sup>19</sup> It has been suggested that members of such families are predisposed to developing upper airway obstruction due to genetic risk factors including obesity, craniofacial morphology, and an abnormality of ventilatory and respiratory muscle control.<sup>78 79 83</sup> In some families subtle craniofacial anatomical abnormalities have been detected and differences in the ventilatory responses to hypoxia and hypercapnia have been found when compared with controls.

More recently a co-aggregation of familial OSA with SIDS and ALTE in infants was identified within families.<sup>84 85</sup> Tishler and colleagues<sup>84</sup> found that 10 of 91 families with OSA studied had at least one case of sudden unexpected infant death or ALTE, whereas there were no such cases in control families with no OSA. Similarly, Mathur and Douglas<sup>85</sup> reported, from a mailed questionnaire, that SIDS occurred more commonly in families that had members with OSA than in control families. It has previously been shown that ALTE and SIDS aggregates within some families, and abnormalities in the sleep and breathing patterns of these infants have been recorded.<sup>86</sup> Guilleminault *et al*<sup>87</sup> presented five families with at least two cases of SIDS and/or ALTE and adult OSA among their family members. It was found that infants in these families had OSA which persisted into childhood. A small airway was a common feature in the members of these families. Recently we have examined the incidence of OSA in infants who have multiple cases of SIDS, ALTE, and/or adult OSA among family members.<sup>88</sup> We found that the majority of infants who had a family history of multiple cases of SIDS, ALTE and/or adult OSA had OSA recorded during infancy, whereas only about one third of infants with a single case of SIDS or ALTE within their family and no OSA in adult family members had OSA. We hypothesised that these infants were possibly genetically predisposed to develop OSA. It is therefore possible that these infants

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will be predisposed to developing OSA later in life.

An abnormal central ventilatory control as well as craniofacial morphology have been proposed as risk factors for familial OSA, and these features are believed to be at least partly genetically determined.<sup>89</sup> Pillar *et al*<sup>90</sup> showed that healthy offspring of patients with OSA were more likely to collapse their airway with loaded breathing than normal controls. Redline *et al*<sup>91</sup> showed that ventilatory responsiveness to hypoxia and hypercapnia was depressed in family members of OSA patients. In addition, a depressed response to hypoxia has been recorded in the siblings of infants with SIDS<sup>92</sup> and also in the parents of SIDS victims.<sup>93</sup>

There is significant evidence that familial factors probably influence the risk of developing OSA in adulthood. Adult physicians and paediatricians should consider looking for the presence of OSA symptoms in relatives of their patients. Information from these patients will provide a better understanding of the development of OSA, may identify patients with familial features who are at risk of developing the OSA syndrome, and could prevent OSA and its consequences in some cases.<sup>79 94</sup>

## ► Conclusions and future research

Infantile and childhood OSA is probably related to the adult OSA syndrome and the possibility of developing OSA during adulthood might be predicted during childhood. The anatomical abnormalities that predispose an individual to OSA are similar across the age groups. The findings of the familial OSA syndrome and its association with SIDS, ALTE and infantile OSA suggest further that adult OSA may be predetermined during infancy or childhood. There is little evidence, however, that adults with OSA had sleep disordered breathing during infancy and/or childhood. Continued contact with the infants that we have studied during the next several years may document the development of OSA in children and adults. In addition, population studies in infants and children are necessary to determine the prevalence and extent of the disease in the paediatric population. Although some investigators believe the OSA syndromes in infants, children and adults could be viewed as three separate syndromes, we believe that they represent different developmental stages in the progression of OSA from infancy to adulthood.

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